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REMARKS

I. Introductory Comments

Claims 10-26 and 35-39 are currently pending in the application. Claims 1-9, 27-34, and 40-49 have been canceled pursuant to the Examiner's restriction requirement. Claims 19-26 have been cancelled without prejudice. Claims 37-39 have been amended. Claims 50-52 are newly added. Reconsideration of the Application is respectfully requested.

II. Examiner Interview Summary

The undersigned thanks Examiner Chen for the courtesies extended during the telephone interview conducted on December 20, 2006. During the interview, the undersigned discussed the "That which is claimed:" statement currently found on page 43 of the specification. Applicants will amend the specification to include a "That which is claimed:" statement on the same page as the first claim. Applicants indicated their intent to cancel claims 19-26 without prejudice. Then the undersigned discussed claims 10-18 and 35-39 with the Examiner.

The undersigned discussed claims 10-18 and 35-39 with regards to the assertion throughout the October 6, 2006 Office Action that the specification fails to disclose any phenotype of the claimed transgenic rabbit. The undersigned presented a discussion of claim 18 which recites the limitation of "altered myosin isoform expression" and the data throughout the specification. The Examiner graciously concurred that the data indicate transgenic rabbits of the invention exhibit altered myosin isoform expression. Next the data in Figure 6 and the Experimental Details indicating the transgenic rabbits exhibit altered cardiac contractility were reviewed. The Examiner graciously indicated that he would consider amendments of the claims in light of the discussion. The undersigned then discussed potential amendments. The Examiner graciously indicated that an amendment including the limitation of "altered cardiac contractility" would be particularly useful with regards to overcoming the §101/§112 utility rejection and possibly the §102 rejections.

The undersigned presented a description of the functional limitation provided by limiting the claim to those nucleotide sequences having at least 90% identity to SEQ ID NO:1 or SEQ ID NO:2, wherein the nucleotide sequence is capable of initiating transcription in an animal cell.

The undersigned and the examiner discussed the functional limitation provided by the limitation of the promoter to those wherein the nucleotide sequence is capable of initiating transcription in an animal cell. While no agreement with respect to this topic was reached, the Applicants appreciate the Examiner's insight.

Applicants gratefully acknowledge Examiners Chen' gracious indication that the specification is enabling for the subject matter of claim 39.

III. Objections to the Specification

The October 6, 2006 Office Action objects to the specification as allegedly lacking the beginning of the claim sentence, that is lacking "That which is claimed." Applicant respectfully draws the Examiner's attention to page 43 of the originally filed specification and the phrase "That which is claimed:" located just below paragraph [0128]. During the course of the December 20, 2006 Examiner's Interview, the undersigned and Examiner Chen discussed this objection. Examiner Chen graciously indicated that an amendment to the claims relocating the phrase "That which is claimed:" to the same page as the first claim would be favorably considered. In light of said amendment, reconsideration and withdrawal of this objection is respectfully requested.

The October 6, 2006 Office Action advises that should claim 12 be found to be allowable, claim 16 will be objected to under 37 CFR §1.75 as being a substantial duplicate thereof. Additionally the October 6, 2006 Office Action advises that should claim 21 be found to be allowable, claim 25 will be objected to under 37 CFR §1.75 as being a substantial duplicate thereof. Applicant notes that in the fields of biology and biotechnology "transcription" is term describing a discrete biological process. Nonetheless, upon allowance of claim 12, Applicant will cancel claim 16. Claims 19-25 have been cancelled thus rendering the objection to claims 21 and 25 moot. Withdrawal of the objections is respectfully requested.

IV. Rejections under 35 U.S.C. § 101

Claims 19-25 are rejected under 35 U.S.C. §101 as allegedly being directed to non-statutory subject matter. Applicant acknowledges and appreciates the guidance provided in the October 6, 2006 Office Action for overcoming this rejection. However, claims 19-25 have been cancelled without prejudice thus rendering this rejection moot.

V. Rejections under 35 U.S.C. § 112, second paragraph

Claims 10-26, 36, and 38 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Office Action alleges that the term "capable of" in claims 10, 11, 18-20, 36 and 38 is vague and renders these claims and the claims depending from these claims indefinite. This rejection is respectfully traversed. The term "capable of" is used in its ordinary plain meaning such as the meaning found in the Random House Unabridged Dictionary 2006 "having the ability or capacity for". *Dictionary.com Unabridged (v 1.0.1)*. Retrieved November 12, 2006, from Dictionary.com website: http://dictionary.reference.com/search?r=2&q=capable. This definition is consistent with Applicants' intention to claim variants of the promoter sequences set forth in SEQ ID NOS:1 and 2 that have at least 90% identity and have the capacity of initiating transcription. Reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph, rejections of record for claims 10, 11, 18, 36 and 38 are respectfully requested.

VI. Rejections under 35 U.S.C. §101 and 35 U.S.C. §112

Claims 10-26 and 35-39 are rejected under 35 U.S.C. §101 as allegedly lacking either a specific and substantial asserted utility or a well-established utility. Claims 10-26 and 35-39 are further rejected under 35 U.S.C. §112 as allegedly failing to teach one of skill in the art how to use the claimed invention. As claims 19-26 have been cancelled the rejection with regards to those claims is moot; the alleged lack of utility with regards to claims 10-18, 35-39, and newly added claims 50-52 will be discussed here below.

Transgenic rabbits of the invention find use at least in "studying heart disease and conditions" [¶0007, instant specification], as the transgenic rabbits of the invention exhibit an

altered cardiopathic phenotype, such as an increased or decreased susceptibility to cardiopathy [¶0095, instant specification]. Further these transgenic rabbits can be used "to identify anti-cardiopathic compounds" and a means of using these transgenic rabbits to identify anti-cardiopathic compounds is described [¶0098-0100, p.34-35, instant specification]. Clearly the specification provides a specific and substantial utility and teaches one skilled in the art how to use the claimed invention. For at least these reasons, reconsideration and withdrawal of the 35 U.S.C. §101/35 U.S.C. §112 rejections of claims 10-18 and 35-39 are respectfully requested.

Claims 37 and 38 have been amended to include the limitation that the transgenic rabbits "exhibit an altered susceptibility to cardiopathy". Support for this amendment is found throughout the specification and particularly in claims 32 and 44. Newly added claim 50 recites language that limits the claimed transgenic rabbits to those that "exhibit an altered susceptibility to cardiopathy." Newly added claim 52 is directed toward transgenic rabbits comprising an expression cassette comprising a promoter having the nucleotide sequence set forth in SEQ ID NO:2 and fragments and variants thereof operably linked to a heterologous nucleotide sequence and that "exhibit an altered susceptibility to cardiopathy". The requirement that transgenic rabbits of the invention "exhibit an altered susceptibility to cardiopathy" provides a clear correlation between the claimed transgenic rabbits and cardiopathy. Rabbits with an altered susceptibility to cardiopathy are of use in studying heart disease, conditions, and treatments. One skilled in the art would clearly know how to use a transgenic rabbit that exhibits altered susceptibility to cardiopathy. Thus reconsideration and withdrawal of the 35 U.S.C. §101/35 U.S.C. §112 rejections of claims 37-38 is respectfully requested.

Claim 39 has been amended to recite the "altered cardiac contractility" phenotype exhibited by the claimed transgenic rabbits. Support for the amendment is found throughout the specification and particularly in figures 5 and 6 and in ¶55 on page 20. Newly added claim 51 recites the "altered cardiac contractility" phenotype of the claimed transgenic rabbits. The Examiner's attention is respectfully drawn to Figures 2, 3, 5 and 6 (pages 5 and 6, current specification) and the experimental details set forth on pages 40-42 of the specification. Briefly the data in Figures 2, 3, 5, and 6 indicate that the ventricles of the transgenic rabbits express both the β and α-myosin heavy chain (MHC) isoforms unlike non-transgenic rabbit ventricles in

which the β-MHC isoform predominates. Cardiomyocytes from transgenic and non-transgenic ventricles exhibit altered actin-activated ATPase activity (Figure 3), and finally, transgenic rabbits exhibit altered cardiac contractility (Figures 5 and 6). Applicant appreciates the Examiner's acknowledgement of the evidence that the transgenic rabbits of claims 39 and 51 exhibit an altered cardiac contractility phenotype during the December 20, 2006 Examiner's Interview and his gracious indication that amendments reciting the phrase "altered cardiac contractility" would be considered.

Transgenic rabbits that exhibit an altered cardiac contractility possess clear utility in studying heart disease and conditions. Further these transgenic rabbits can be used "to identify anti-cardiopathic compounds" and a means of using these transgenic rabbits to identify anti-cardiopathic compounds is described [¶0098-0100, p.34-35, instant specification]. Clearly the specification provides a specific and substantial utility and teaches one skilled in the art how to use the claimed invention. Thus, this ground of rejection has been overcome by the amendments to claims 39 and the incorporation of the "altered cardiac contractility" language in newly added claim 51. Reconsideration and withdrawal of the 35 U.S.C. §101/35 U.S.C. §112 rejections of claim 39 as amended are respectfully requested.

V. Rejections under 35 U.S.C. §112

Claims 10-26 and 35-38 are rejected under 35 U.S.C §112 as allegedly failing to comply with the written description requirement. The Office Action alleges that the specification does not describe the claimed subject matter in such away as to convey to one skilled in the art that the inventor had possession of the claimed invention. The Office Action alleges that the specification does not disclose any phenotype associated with the transgenic rabbits of the invention and that the claims encompass numerous transgenic rabbits and animals having various unknown and unidentified phenotypes or no phenotype. The alleged absence of phenotype "is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed" invention (October 6, 2006 Office Action p. 9). Claims 19-26, reading on transgenic animals, have been cancelled without prejudice. Claims 10-18 and 35-38 read on transgenic rabbits comprising an expression cassette comprising a promoter having the sequence

set forth in SEQ ID NO:1 or SEQ ID NO:2 or a fragment or variant thereof operably linked to a heterologous nucleotide sequence.

The October 6, 2006 Office Action alleges that "[t]he specification fails to disclose any phenotype of the claimed transgenic ...rabbits" (page 9); however, the specification provides guidance as to the phenotype of the claimed transgenic rabbits. As seen below many of the claims recite phenotypes that the claimed transgenic rabbits exhibit.

Claims 15 and 16 are directed to transgenic rabbits comprising an expression cassette comprising a promoter having a nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:2 or fragments or variants thereof operably linked to a heterologous nucleotide sequence that exhibit the phenotype of altered expression of the heterologous nucleotide sequence.

Newly added claim 50 is directed to transgenic rabbits comprising an expression cassette comprising a promoter having a nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:2 or fragments or variants thereof operably linked to a heterologous nucleotide sequence that exhibit the phenotype of altered susceptibility to cardiopathy.

Claim 18 is directed to transgenic rabbits comprising an expression cassette comprising a promoter having a nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:2 or fragments or variants thereof operably linked to a heterologous nucleotide sequence having the nucleotide sequence set forth in SEQ ID NO:3 or SEQ ID NO:4 or variants thereof that exhibit the phenotype of altered myosin isoform expression.

Newly added claim 51 is directed to transgenic rabbits comprising an expression cassette comprising a promoter having a nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:2 or variants thereof operably linked to a heterologous nucleotide sequence having the nucleotide sequence set forth in SEQ ID NO:3 or SEQ ID NO:4 or variants thereof that exhibit the phenotype of altered cardiac contractility.

Claims 37-38 as amended and newly added claim 52 are directed to transgenic rabbits comprising an expression cassette comprising a promoter having a nucleotide sequence set forth in SEQ ID NO:2 and variants thereof operably linked to a heterologous nucleotide sequence that exhibit the phenotype of an altered susceptibility to cardiopathy. Thus, the disclosure provides "common attributes or characteristics that identify the claimed transgenic" rabbits.

Transgenic rabbits of the invention are described throughout the specification but particularly in Examples 1 and 3-8 describing transgenic rabbits comprising SEQ ID NO:5, the rabbit β-myosin heavy chain promoter operably linked to the α-myosin heavy chain. Data obtained from transgenic rabbits comprising SEQ ID NO:5 and provided in the specification is discussed above herein. Further description of the transgenic rabbits of the invention is provided in Example 2 in which transgenic rabbits comprising SEQ ID NO:2 operably linked to the CAT reporter gene are described. The data in Figure 1 were obtained from CAT expressing transgenic rabbits and clearly indicate that the transgenic rabbits exhibit altered expression of a heterologous nucleotide sequence. The applications specification shows "actual reduction to practice by describing testing of the claimed invention [MPEP 2163 §I, ¶3]", thus demonstrating possession of the claimed invention. Further, the test results described in the specification were obtained from at least two distinct transgenic rabbit strains or species, the CAT expressing rabbits and the β-MHC promoter operably linked to α-MHC rabbits. These different transgenic rabbit strains provide the requisite representative number of species to support the claims to the claimed genus of transgenic rabbits. Therefore, for at least the reasons set forth herein, claims 10-18, 35-38 and newly added claims 50-52 are adequately described. Reconsideration and withdrawal of the 35 U.S.C. §112 written description rejection are respectfully requested.

Claims 10-26 and 35-39 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to enable one skilled in the art to make and use the invention. Applicants gratefully note the Examiner's recognition that the "specification discloses generation of a transgenic rabbit comprising the sequence of SEQ ID NO:5 and transgenic rabbit line expressing [the] CAT reporter gene under the control of the beta-myosin heavy chain promoter (SEQ ID NO:2)" (Office Action, October 6, pp 10-11). Applicants appreciate the Examiner's indication that the specification is enabling for the transgenic rabbits of claim 39 (December 20, 2006, Examiner's Interview). Nonetheless the Office Action alleges that the "specification fails to provide adequate guidance and evidence for how to make the claimed transgenic [...] rabbits" and that the specification "fails to disclose any phenotype of the claimed transgenic [...] rabbits." Applicants respectfully draw the Examiner's attention to Example 1 (page 39 of the

specification). Example 1 provides specific detailed discussion of a method of making the claimed transgenic rabbits; methods of making transgenic rabbits are discussed on pages 28-30 of the specification also. Thus the specification provides at least adequate guidance and evidence for how to make the claimed transgenic rabbits. With regards to the alleged lack of disclosure of a phenotype, the Examiner's attention is respectfully redirected to the above discussion of phenotypes associated with the transgenic rabbits. As noted therein, the transgenic rabbits of claims 15, 16, 18, 37-39 as amended, and newly added claims 50-52 are associated with phenotypes of altered expression of the heterologous nucleotide sequence, altered susceptibility to cardiopathy, or altered cardiac contractility.

Applicants note the Examiner's gracious acknowledgement that "transgenic ventricle tissue contains both alpha and beta myosin heavy chain isoform (example 6)" (page 11 of the October 6, 2006 Office Action). Further Applicants respectfully draw the Examiner's attention to Figures 5 and 6 and Example 8 of the specification. Figures 5 and 6 present test results obtained from a transgenic rabbit of the invention that indicates that the transgenic rabbits exhibit altered cardiac contractility.

Further the Office Action suggests that "[a] slight change of a promoter sequence could result in dramatically increase or decrease in the transcriptional activity of said promoter" (October 6, 2006 Office Action p14). Claims 35, 37, and 39 are limited to the nucleotide sequences recited by SEQ ID NO: in the claims, thus argument is moot with regards to claims 35, 37, and 39. With regards to claims 10-18, 36, and 38 the claims recite variants that have 90% sequence identity and with the functional limitation of "being capable of initiating transcription in an animal cell." Clearly the claimed invention does not require undue experimentation, rather the claimed invention reduces undue experimentation when there is a desire to express an exogenous nucleotide sequence of interest in the cardiac tissue of a rabbit.

In summary, claims 37-39 have been amended to more clearly recite the phenotype associated with the transgenic rabbits and newly added claims 50-52 incorporate the phenotype linked to transgenic rabbits. The specification clearly teaches at least one method of making the claimed transgenic rabbits. For at least these reasons, claims 10-18, 35-36, 37-39 as amended,

and newly added claims 50-52 are adequately enabled, and it is respectfully requested that the 35 U.S.C. §112, first paragraph rejection of record be reconsidered and withdrawn.

V. Rejections under 35 U.S.C. §102 or 35 U.S.C. §103

Claims 10-13, 15, 16, 19-22, and 24-26 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by, or in the alternative, under 35 U.S.C. 103(a) allegedly obvious over Marian *et al* 1999 *J. Clinical Investigation* 104:12 1683-1692. Claims 19-22 and 24-26 have been cancelled without prejudice. The remaining rejections of claims 10-13, 15 and 16 are respectfully traversed for the reasons set forth below.

Marian describes a transgenic rabbit comprising a murine beta-myosin heavy chain promoter linked to human beta-myosin heavy chain cDNA that exhibited no gross or microscopic phenotype. The Office Action states "It is very likely that the 7kb murine beta-myosin heavy chain promoter has at least 50 contiguous nucleotides of SEQ ID NO:1 or SEQ ID NO:2, therefore the claims are anticipated by Marian." (p17, October 6, 2006 Office Action). The applicant respectfully traverses this rationale.

"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" [MPEP 2112, §IV]. The assertion that "it is very likely" that a characteristic such as at least 50 contiguous nucleotides of SEQ ID NO:1 or SEQ ID NO:2 is present in the 7kb murine β-MHC promoter utilized in Marian does not establish the existence that characteristic in the prior art. Rather, "[t]he Examiner must provide a basis in fact... to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy* 17 USPQ2d 1461, 1464 BPAI 1990). The Office Action recognizes the uncertainty of the existence of at least 50 contiguous nucleotides of SEQ ID NO:1 or SEQ ID NO:2 in the 7kb murine β-MHC promoter on page 17: "If the 7kb murine beta-myosin heavy chain promoter does not have at least 50 contiguous nucleotides of SEQ ID NO:1 or 2..." In the absence of evidence that the 7kb murine β-MHC promoter of Marian comprises at least 50 contiguous nucleotides of SEQ ID NO:1 or 2, it is respectfully requested that the 35 U.S.C. §102(b) rejection of record be withdrawn.

If the 7kb murine beta-myosin heavy chain promoter of Marian does not have at least 50 contiguous nucleotides of SEQ ID NO:1 or 2 the Office Action alleges it would have been obvious to make the claimed transgenic rabbit according to the teaching of Marian especially because "no phenotype is needed in the claimed transgenic animal or rabbit." The applicant respectfully disagrees. The transgenic rabbits of Marian differ significantly from the claimed transgenic rabbits of claims 10-13, 15 and 16. The rabbits of Marian comprise a murine beta-myosin heavy chain promoter linked to human beta-myosin heavy chain cDNA; the claimed rabbits comprise a rabbit beta-myosin heavy chain promoter (SEQ ID NO:2) or a rabbit alpha-myosin heavy chain promoter (SEQ ID NO:1) operably linked to a heterologous nucleotide sequence. In addition to the promoter differences between the claimed transgenic rabbits and the transgenic rabbits of Marian, Marian provides no teaching, suggestion or motivation to develop the claimed transgenic rabbits. According to the Office Action, the transgenic rabbits of Marian do not provide "a specific and substantial utility or well-established utility" [page 7, October 6, 2006 Office Action]. In light of Marian's results, there appears to be no suggestion to pursue development of the claimed transgenic rabbits. Thus, it is respectfully requested that the 35 U.S.C. §103 rejection of claims 10-13, 15, and 16 be reconsidered and withdrawn.

VI. Rejections under 35 U.S.C. §102

Claims 10-26 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by James *et al.* 2000 (*Circulation* 101:1715-1721). Claims 19-26 have been cancelled without prejudice. The rejection of claims 10-18 is respectfully traversed for the following reasons.

James teaches making transgenic rabbits using murine alpha or beta myosin heavy chain promoter operably linked to a nucleotide sequence encoding CAT. The CAT nucleotide sequence is a heterologous nucleotide sequence. The mouse alpha-MHC and beta-MHC promoters are about 85% identical to the respective rabbit promoters in the proximal 600 base pair. Thus, alleges the Office Action, the mouse alpha MHC and betaMHC promoters would comprise at least 50 contiguous nucleotides of SEQ ID NO:1 and SEQ ID NO:2 respectively. The Applicant respectfully disagrees.

"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" [MPEP 2112, §IV]. The assertion that the murine promoters utilized in James would comprise at least 50 contiguous nucleotides of the nucleotide sequences of SEQ ID NO:1 or SEQ ID NO:2 respectively does not establish the existence of that characteristic in the prior art. Rather, "[t]he Examiner must provide a basis in fact... to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy* 17 USPQ2d 1461, 1464 BPAI 1990). In the absence of evidence that the murine promoters of James comprise at least 50 contiguous nucleotides of SEQ ID NO:1 or 2, it is respectfully requested that the 35 U.S.C. §102(b) rejection of record be withdrawn for claims 10-18.

In addition, claim 17 specifies that the heterologous nucleotide sequence comprises a nucleotide sequence set forth in SEQ ID NO:3 (alpha-MHC) or SEQ ID NO:4 (beta-MHC) or variants thereof. Claim 18 depends from claim 17 and further specifies that the rabbit exhibits altered myosin isoform expression. Although James teaches transgenic rabbits comprising mouse MHC promoters operably linked to the CAT reporter gene, a heterologous nucleotide sequence, James does not teach a heterologous nucleotide sequence comprising alpha-MHC or beta-MHC. As James does not teach every element of claims 17 and 18, James does not anticipate claims 17 and 18 for at least these additional reasons. Therefore, Applicants respectfully request that the 35 U.S.C. §102(b) rejection be reconsidered and withdrawn for claims 17 and 18.

VII Newly Added Claims

New claim 50 incorporates all the elements and limitations of claims 10 and 32. New claim 51 incorporates all the elements and limitations of claims 17 and recites the phenotype of "altered cardiac contractility". Support for the phenotype element is found throughout the specification and particularly in figures 5 and 6 and in ¶55 (page 20, specification). In addition to the phenotypic element discussed elsewhere herein, newly added claim 52 recites that the claimed fragments and variants of SEQ ID NO:2 have at least 95% identity to the nucleotide sequence set forth in SEQ ID NO:2 or have at least 100 contiguous nucleotides of the nucleotide

sequence set forth in SEQ ID NO:2 and retain the capability of initiating ventricle-preferred transcription in a rabbit cell. Support for these elements can be found throughout the specification and particularly in ¶¶29 and 30 (pages 10-11 of the specification). It is respectfully submitted that sufficient basis for these claims is present in the application as originally filed.

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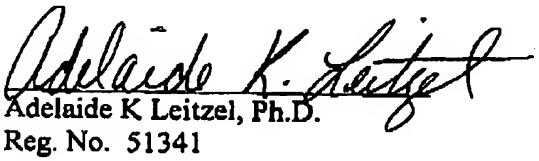
VIII Conclusion

In light of the foregoing, it is respectfully submitted that claims 10-18, 35-36, 37-39 as amended, now pending, and newly added claims 50-52 are in condition for allowance. Reconsideration and withdrawal of the rejections of record are respectfully requested.

The Commissioner is hereby authorized to charge any additional fees that may be required by this paper, or to credit any overpayment to Deposit Account 50-3072. If the Examiner wishes to discuss any aspect of this response, do not hesitate to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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